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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,620	06/27/2007	Jonni Moore	P-7671-US	5253

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EXAMINER	
MARTIN, PAUL C	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,620	MOORE ET AL.	
	Examiner	Art Unit	
	PAUL C. MARTIN	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending in this application.

Election/Restrictions

Applicant's election of Group I (Claims 1-13) in the reply filed on 04/24/09 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 14-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-13 were examined on their merits.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Figure 2 (M1 and M2).

Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The use of the trademarks TO-PRO™ and ORACLE™ has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1, step c contains a misspelling of the term "proliferation". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7 and 8 recite the limitation "cell surface marker". Further, Claim 8 recites the limitation "CD8". There is insufficient antecedent basis for these limitations in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-9, 12 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over McCabe *et al.* (2001) in view of Nygaard *et al.* (2002).

McCabe *et al.* teach a method comprising the steps of; enriching a subpopulation of murine leukocytes ($CD4^+$ T-cells) from splenocytes using the fluorescent cell surface marker anti-CD4-FITC, staining the enriched $CD4^+$ T-cells with the intracellular protein stain CFSE, contacting a test population of CFSE stained $CD4^+$ T-cells with lead (Pb)-glutamate sufficient to stimulate proliferation; and measuring the loss of CFSE staining as compared to a control population of $CD4^+$ T-cells, wherein loss of staining indicates cellular proliferation (Pg. 221, Column 2, Lines 6-28 and Pg. 224, Column 1, Lines 1-27 and Column 2, Lines 1-9 and Table 2 and Pg. 225, Fig. 5).

McCabe *et al.* further teaches that $CD8^+$ cells in lead exposed allogenic-mixed lymphocyte cells (MLC) also exhibit enhanced proliferation and that the functional consequences of lead enhancement of $CD4^+$ and $CD8^+$ interactions as well as the influences of lead on the repertoire of cytotoxic T lymphocytes warrants consideration (Pg. 229, Column 2, Lines 20-29).

McCabe *et al.* teaches that it was known in the art that *in vitro* Pb exposure induces immune dysfunction such as increased Th2 cell proliferation, impaired Th1 proliferation, increased production of Th2-derived cytokines and inhibited production of Th1-derived cytokines and enhances the development of Th2 cells and impairs Th1-mediated immune effector functions *in vivo*. Therefore, it is inherent in the method of McCabe *et al.* that $CD4^+$ cells exhibiting a loss of CFSE staining indicative of proliferation would also be indicative of a murine subject that is sensitive to lead. The determination of metal-sensitivity constitutes a mental step or conclusion on the part of the artisan performing the method.

McCabe *et al.* does not teach a method wherein the leukocytes are peripheral blood leukocytes (PBL) or wherein the step of selecting a subpopulation of said PBL comprises using the cell surface marker CD8.

Nygaard *et al.* teach the advantageous use of murine blood lymphocytes over the use of murine spleen lymphocytes in immunotoxic assays, such as that blood lymphocytes may be more relevant for comparison with results from human peripheral lymphocytes resulting in improved extrapolation of findings from murine to man, that blood lymphocytes may be a more sensitive indicator of immunotoxic effects than spleen cells and that repeated collection of peripheral blood samples from the same animals will be possible, thereby possibly reducing experimental variation and reducing the number of sacrificed animals (Pg. 153, Column 2, Lines 1-12 and Pg. 154, Column 1, Lines 1-5).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method for determining the effects of lead on splenocyte isolated lymphocyte proliferation as taught by McCabe *et al.* by using peripheral blood lymphocytes as taught by Nygaard *et al.* because immunotoxicological studies are performed by measuring the effects of chemical substances on lymphocytes (such as lead exposure) *in vitro* and/or *in vivo*. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of determining the effects of lead on isolated splenocyte isolated $CD4^+$ lymphocyte proliferation as taught by McCabe *et al.* to use CD8 as the sell surface marker for subpopulation selection because McCabe *et al.* teaches that $CD4^+$ cells and $CD8^+$ cells are observed to have enhanced proliferation in response to lead exposure and the reference further suggests that further investigation is required.

One of ordinary skill in the art would have been motivated to make the modification to use PBL instead of splenocyte lymphocytes because of the advantages taught by Nygaard *et al.* above such as more relevant data extrapolation from murine to man, increased sensitivity and reduced variability and animal sacrifice. One of ordinary skill in the art would have been motivated to use $CD8^+$ cell surface markers as opposed to $CD4^+$ because both cell markers show enhanced proliferation in response to lead and would therefore be recognized as functional equivalents in determining lymphocyte proliferation. There would have been a reasonable expectation of success in making these modifications because the McCabe *et al.* reference recognizes $CD8^+$ as having similar properties to $CD4^+$ expressing lymphocytes and because both the McCabe *et al.* and Nygaard *et al.* references are drawn to similar fields of endeavor, which is the use of murine lymphocytes in immunotoxicological study.

Claims 1-13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fontenot *et al.* (2003).

Fontenot *et al.* teaches a method wherein peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage (BAL) cells from subjects diagnosed with chronic beryllium disease (CBD) are stained with monoclonal antibodies to CD4, CD8 and CD28 in order to identify the lymphocyte (T-cell) population (Pg. 777, Column 1, Lines 15-34 and Column 2, Lines 25-27); contacting the identified BAL T-cell supopulation with the intracellular protein stain CFSE (Pg. 777, Column 1, Lines 36-37); contacting the BAL $CD4^+$ T-cells with 100 μM Beryllium sulfate ($BeSO_4$); and measuring the loss of in fluorescence intensity indicative of proliferation and CBD subject sensitivity to beryllium (Pg. 781, Fig. 7A) and wherein a confirming thymidine incorporation proliferation assay also showed increased proliferation in sorted $CD4^+$ cells from a CBD subject, which were exposed to 100 μM $BeSO_4$ as compared to control indicative of sensitivity to beryllium in the CBD subject (Pg. 781, Fig. 7B) and wherein both PBMC and BAL T-cells from CBD subjects are used in beryllium exposure experiments (Pg. 780, Fig. 5).

Fontenot *et al.* does not teach a method wherein PBL are used with CFSE in a beryllium sensitivity assay.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Fontenot *et al.* wherein BAL T-Cells are stained with CFSE in order to measure proliferation due to exposure to beryllium by substituting PBL T-cells for BAL cells because the reference teaches the use of both types of cells in beryllium exposure assays and one of ordinary skill in the art would have recognized that the cell types were art-recognized equivalents. The MPEP states:

> In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958)

One of ordinary skill in the art would have been motivated to make this substitution because the inherent advantages of using blood derived lymphocytes as opposed to BAL derived lymphocytes. Obtaining blood lymphocytes only requires a simple draw blood from a subject whereas BAL is a medical procedure requiring passing a bronchoscope through the mouth or nose of a subject and into the lung. There would have been a reasonable expectation of success in making this substitution as the reference teaches the use of both types of lymphocytes.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Fontenot *et al.* (US 2006/0263761 A1).

Fontenot *et al.* "Target organ localization of memory $CD4^+$ cells in patients with chronic beryllium disease"; The Journal of Clinical Investigation, Vol. 110, No. 10 (2002) pp. 1473-1482.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL C. MARTIN whose telephone number is (571)272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin
Examiner
Art Unit 1657

06/02/09

/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657